

PB86-134129

Health Effects
Assessment for Hexachlorocyclopentadiene

(U.S.) Environmental Protection Agency
Cincinnati, OH

Sep 84



U.S. Department of Commerce
National Technical Information Service

NTIS

HEALTH EFFECTS ASSESSMENT
FOR HEXACHLOROCYCLOPENTADIENE

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
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Washington, DC 20460

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SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA <i>(Please read Instructions on the reverse before completing)</i>		
1. REPORT NO. EPA/540/1-86/001	2.	3. RECIPIENT'S ACCESSION NO. PB86 1341297AS
4. TITLE AND SUBTITLE Health Effects Assessment for Hexachlorocyclopentadiene	5. REPORT DATE September 1984	
	6. PERFORMING ORGANIZATION CODE EPA/600/22	
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.	
9. PERFORMING ORGANIZATION NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	10. PROGRAM ELEMENT NO.	
	11. CONTRACT/GRANT NO.	
12. SPONSORING AGENCY NAME AND ADDRESS Office of Emergency and Remedial Response Office of Solid Waste and Emergency Response U.S. Environmental Protection Agency Washington, DC 20460	13. TYPE OF REPORT AND PERIOD COVERED	
	14. SPONSORING AGENCY CODE	
15. SUPPLEMENTARY NOTES		
16. ABSTRACT This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes. A subchronic and chronic interim acceptable intake was determined for hexachlorocyclopentadiene based on both oral and inhalation exposure.		
17. KEY WORDS AND DOCUMENT ANALYSIS		
a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 46
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with hexachlorocyclopentadiene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria for Hexachlorocyclopentadiene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-055. NTIS PB 81-117667.

U.S. EPA. 1984. Health Assessment Document for Hexachlorocyclopentadiene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-001F. NTIS PB 85-124915.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q₁*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Subchronic oral exposure data are limited. Ninety day exposures of rats and mice indicated that rats are more sensitive to HEX toxicity than mice. Both species showed lesions of the forestomach at their respective LOAELs. Using the rat data, an AIS for oral exposure of 4.9 mg/day is estimated. In the absence of chronic oral exposure data, an AIC of 0.49 mg/day for the oral route is estimated by applying an additional uncertainty factor of 10 to the AIS.

Subchronic inhalation data are also limited. Rats and monkeys have been tested for periods up to 14 weeks. Using the monkey data, an inhalation AIS of 0.2 mg/day is estimated.

Chronic inhalation evaluations of HEX have been conducted in guinea pigs, rabbits, rats and mice. Data are of limited use, except for the rat, because of incomplete reporting of results and questions concerning the purity of the compound. However, the data are adequate to raise questions concerning interspecies differences in sensitivity to this compound. An inhalation AIC of 0.0046 mg/day is estimated based on the rat data of Clark et al. (1982a). This estimate is lower than an estimate which could be derived from the TLV. Despite questions concerning available data, the incorporation of uncertainty factors should provide an adequate margin of safety. These estimates should be reviewed when more complete data are available. A CS of 62 was calculated based on mortality in mice exposed to 1.7 mg/m³, 7 hours/day, 5 days/week, for as many as 150 treatments.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

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Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CS	Composite score
DNA	Deoxyribonucleic acid
FEL	Frank-effect level
GC/MS	Gas chromatography/mass spectrometry
LD ₅	Dose lethal to 5% of recipients
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
RV _d	Dose-rating value
RV _e	Effect-rating value
SMR	Standardized mortality ratio
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Hexachlorocyclopentadiene (HEX) is the most commonly used name for the compound that is designated 1,2,3,4,5,5'-hexachloro-1,3-cyclopentadiene by the International Union of Pure and Applied Chemistry system (IUPAC). Table 1-1 cites the IUPAC name and synonyms, the Chemical Abstract number and molecular and structural formulas for HEX.

Hexachlorocyclopentadiene is a nonflammable liquid with a characteristic pungent, musty odor; the pure compound is light lemon-yellow. Table 1-2 presents the physical properties and constants for HEX.

Commercial HEX has various purities depending upon the route of synthesis. HEX is a highly reactive diene that readily undergoes addition and substitution reactions and also participates in Diels-Alder reaction of HEX with a compound containing a nonconjugated double bond consisting of 1:1 adducts containing a hexachlorobicyclo (2,2,1) heptene structure; the monene derived part of the adduct is nearly always in the endo position. Figure 1-1 illustrates synthetic pathways to various chlorinated pesticides for which HEX is a precursor. HEX may be present in these pesticides as a contaminant.

HEX is released into the environment during its manufacture and during the manufacture of products requiring HEX. Limited monitoring data from production sites indicated that HEX was present at 18 mg/l in the aqueous discharge from the Memphis pesticide plant (U.S. EPA, 1984).

In May 1977, HEX was also detected at 0.17 mg/l in the aqueous discharge and at 56 ppb in air samples collected from a waste site in Montague, MI (U.S. EPA, 1984). At a waste site in Hardeman County, TN, HEX has been shown to be emitted into the air, groundwater, wastewater and drinking water (Clark et al., 1982b). Indoor air concentrations of HEX in houses with contaminated groundwater supplies ranged from 0.06-0.10 $\mu\text{g}/\text{m}^3$.

TABLE 1-1
Identity of Hexachlorocyclopentadiene*

Identifying Characteristic	Name/Number/Structure
IUPAC Name:	1,2,3,4,5,5'-Hexachloro-1,3-cyclopentadiene
Trade Names:	C56; HRS 1655; Graphlox
Synonyms:	Hexachlorocyclopentadiene Perchlorocyclopentadiene HEX HCPD HCCP HCCPD C-56 HRS 1655 Graphlox
CAS Number	77-47-4
CIS Accession Number:	7800117
Molecular Formula:	C ₅ Cl ₆
Molecular Structure:	

*Source: Stevens, 1979

TABLE 1-2
Physical Properties of Hexachlorocyclopentadiene

Property	Value/Description	Reference
Molecular Weight:	272.79	Stevens, 1979
Physical Form (25°C)	Pale yellow liquid	Hawley, 1977; Irish, 1963
Odor:	Pungent	Hawley, 1977; Irish, 1963
Electronic Absorption Maximum (in 50% acetonitrile-water)	322 nm	Wolfe et al., 1982
Solubility		
Water (mg/l):	2.1 (25°C) 0.805 (25°C) 1.8 (28°C)	Da1 Monte and Yu, 1977 Lu et al., 1975 Wolfe et al., 1982
Organic Solvents:	Miscible (Hexane)	Bell et al., 1978
Vapor Density (air = 1)	9.4	Verschueren, 1977
Vapor Pressure (mmHg, °C):	0.08 (25°C) 0.975 (62°C)	Irish, 1963 Stevens, 1979
Specific Gravity:	1.717 (15°C) 1.710 (20°C) 1.7019 (25°C)	Hawley, 1977 Stevens, 1979 Weast and Astle, 1980
Melting Point (°C):	-9.6 -11.34	Hawley, 1977 Stevens, 1979
Boiling Point (°C):	239 @ 753 mm Hg 234	Hawley, 1977; Stevens, 1979 Irish, 1963
Octanol/Water Partition Coefficient (log P) (measured): (estimated):	5.04±0.04 5.51	Wolfe et al., 1982 Wolfe et al., 1982
Latent Heat of Vaporiza- tion	176.6 J/g	Stevens, 1979
Henry's Law Constant (atm-m ³ /mole)	2.7×10 ⁻²	Atallah et al., 1980; Wolfe et al., 1982

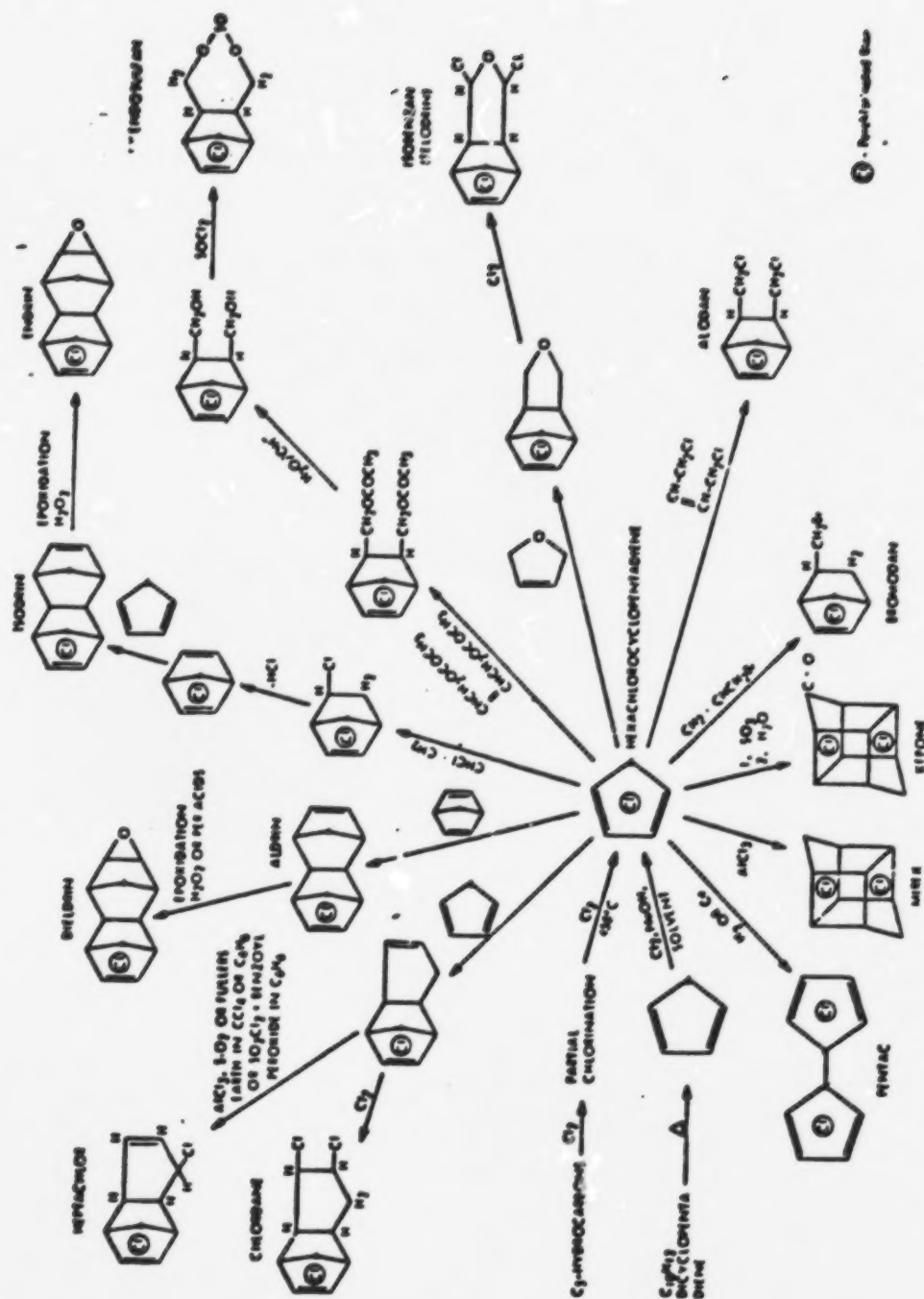


FIGURE 1-1
Syntheses of Chlorinated Cycloclene Pesticides from Hexachlorocyclopentadiene

Source: U.S. EPA, 1984

Published reports, environmental releases and physiochemical properties of HEX imply that it will be present mainly in the aquatic compartment and associated with bottom sediments and organic matter. Relatively much lower concentrations will be found in the soil and air compartments. Air levels in areas near previous dump sites have been shown to be high. High concentrations of HEX have been recorded in wastewater and, in two incidences, have increased the ambient HEX levels inside treatment facilities above the ACGIH TWA.

Little relevant information is available to predict the fate of HEX in air. Its tropospheric residence time was estimated by Cupitt (1980) to be ~5 hours based upon rates of reaction with hydroxyl radicals and ozone. The respective reaction rates were theoretically estimated to be 59×10^{-12} and 8×10^{-10} $\text{cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$. Atmospheric photolysis of HEX was rated as probable, since HEX has a chromophore that absorbs light in the solar spectral and is known to photolyze in aqueous media. Cupitt (1980) listed the theoretical degradation products as Cl_2CO , diacylchlorides, ketones, and free Cl radical, all of which would be likely to react with other elements and compounds.

In the event of release into shallow or flowing bodies of water, degradative processes such as photolysis, hydrolysis and biodegradation, as well as transport processes involving volatilization and other physical loss mechanisms, are expected to be prominent in HEX dissipation.

Under a variety of sunlight conditions, in both distilled and natural waters of 1-4 cm depth, phototransformation half-life was <10 minutes. Addition of sediments to distilled water containing HEX had little effect on the phototransformation rate constant of HEX at this latitude on cloudless

days (averaged over both light and dark periods for a year) that was 3.9 hour^{-1} , corresponding to a half-life of 10.7 minutes (Zepp et al., 1979; Wolfe et al., 1982).

Studies of the hydrolysis of HEX indicate that at 25-30°C and in the environmental pH range of 5-9, a hydrolytic half-life of ~3-11 days is observed (Wolfe et al., 1982). Hydrolysis is much slower than photolysis, but may be a significant load-reducing process in waters where photolysis and physical transport processes are not important (i.e., in deep, nonflowing waters).

Wolfe et al. (1982) found hydrolysis of HEX to be independent of pH over a range of 3-10. With a variation in temperature, these rates changed somewhat.

HEX is not expected to be oxidized under ordinary environmental conditions. Based on an estimated first order oxidation rate constant, a computer simulation predicted that HEX would not be oxidized in the simulated river, pond or eutrophic lake.

Tabak et al. (1981) stated that HEX is biodegraded fairly rapidly in a static laboratory culture. Upon release onto soil, HEX is likely to adsorb strongly to any organic matter or humus present (Kenaga and Goring, 1980; Weber, 1979). With time, HEX concentrations should decrease as populations of soil microorganisms better adapted to metabolize HEX increase (Rieck, 1977a,b,c; Thuma et al., 1978).

The log octanol/water partition coefficient (log P) of HEX has been experimentally determined to be 5.04 (Wolfe et al., 1982) and 5.51 (Veith et al., 1979), which indicates a substantial potential for bioconcentration, bioaccumulation and biomagnification. Actual determinations of bioconcentra-

tion and bioaccumulation in several aquatic organisms indicate that HEX does accumulate to a great extent (Podowski and Khan, 1979; Veith et al., 1979; Spehar et al., 1979).

Veith et al. (1979) determined the BCF for HEX to be 29 in the fathead minnow, P. promelas. Spehar et al. (1979) conducted a 30-day early-life stage, flowthrough toxicity test at 25°C with the fathead minnow. HEX residues in the fish after 30 days of continuous exposure to HEX were <0.1 mg/kg for all concentrations tested (0.78-9.1 µg/l in water). In two other studies (Velsicol Chemical Corporation, 1978; Bennett, 1982), HEX was not detected in any of the fish tissue samples analyzed by GC/MS.

The fate and transport of HEX in the atmosphere are not well documented, but available information suggests that the compound does not persist. In water, HEX is likely to dissipate rapidly by means of photolysis, hydrolysis and biodegradation. Biodegradation may also be a significant process in certain waters, although the evidence is weak. HEX is known to volatilize from water; however, it is possible that volatilization is limited by diffusion, particularly in waters that are not well mixed, and by sorption on sediments.

The fate and transport of HEX in soils are affected by its strong tendency to adsorb onto organic matter. HEX is predicted to be relatively immobile in soil based on its high log P value. Volatilization, which is likely to occur primarily at the soil surface, is inversely related to the organic matter levels and water-holding capacity of the soil. Leaching of HEX by groundwater should be very limited, and chemical hydrolysis and microbial metabolism are expected to reduce environmental levels. HEX is metabolized by a number of soil microorganisms. HEX may be found in areas where there was no HEX production or usage, because it may be present as a contaminant in products made from it.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Absorption rates have not been calculated for HEX. Dorrough (1979) studied the oral absorption of HEX in male and female Sprague-Dawley rats and mice. Although absorption was shown by the presence of the radiolabeled compound in the feces (72%) and urine (14%), the rates were not calculated.

In a study by Yu and Atallah (1981), male and female Sprague-Dawley rats (240-350 g) were given a single dose of 3 or 6 mg/kg ^{14}C -HEX in 0.5 ml corn oil by oral gavage. Radioactivity appeared in the blood within 30 minutes, reached a maximum value at 4 hours, and then gradually decreased. The excretion levels were near the values of Dorrough (1979).

2.2. INHALATION

Dorrough (1980) studied the absorption and fate of inhaled HEX in female Sprague-Dawley rats (175-250 g). Animals were exposed to vapors of ^{14}C -HEX over a 1-hour period to achieve doses of $\sim 24 \mu\text{g/kg bw}$. The radiolabel was recovered in the feces and urine; however, no absorption rates were calculated.

2.3. CONCLUSIONS REGARDING HEX ABSORPTION RATES

From the data reviewed in the pharmacokinetic studies of HEX, the following points can be made regarding the fate of HEX in biological systems:

- HEX reacts with biological tissues and macromolecules at the point of administration as indicated by the high concentration of HEX equivalents in the lung and trachea following inhalation exposure.
- HEX is not readily absorbed through the gastrointestinal tract as indicated by the following: the 2- to 3-fold higher fecal elimination of HEX equivalents following oral administration as compared with intravenous or inhalation administration, and the reactivity of HEX with the gastrointestinal contents as indicated by the fact that no unchanged HEX is excreted following oral administration.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. In a range-finding study, Litton Bionetics Inc. (1978a) determined the oral LD₅ of HEX in Charles River CD-1 rats to be 76 mg/kg. However, when the LD₅ was administered to rats for 5 consecutive days, all 24 animals died. In a comparable range-finding study in Fischer 344 rats (SRI, 1980b) no mortality was reported at doses of 25, 50 or 100 mg/kg when given 12 doses in 16 days.

The subchronic toxicity of HEX is summarized in Table 3-1. In the oral dose studies (Abdo et al., 1984), dose levels of 19, 38, 75, 150 and 300 mg/kg HEX (94.3-97.4% pure) in corn oil were administered by gavage to groups of 10 male and 10 female mice. Doses were administered 5 days/week for 13 weeks. At the highest dose level (300 mg/kg), all male mice died by day 8 and 3 females died by day 14. In female mice, the liver was enlarged. Dose levels of ≥ 38 mg/kg HEX caused lesions in the forestomach, including ulceration in both males and females. At doses of ≥ 75 mg/kg, toxic nephrosis was seen in females. In the rat portion of this study, doses of 10, 19, 38, 75 and 150 mg/kg HEX were administered. Mortality and toxic nephrosis were noted in both males and females at doses of ≥ 38 mg/kg. The male rats treated at 19 mg/kg dose level did not show any highly abnormal effects, while females exhibited lesions of the forestomach. Such lesions were observed in male rats at the ≥ 38 mg/kg dose levels. There was a dose-related depression of body weight gain relative to the controls. The NOAEL for rats was selected to be the 10 mg/kg level.

3.1.2. Inhalation. Rand et al. (1982) and Alexander et al. (1980) performed inhalation studies in rats and monkeys. Groups of 40 male and 40 female Sprague-Dawley rats weighing 160-226 g, or groups of 12 cynomolgus

TABLE 3-1
Subchronic Toxicity of HEX

Study	Species	Dose	Results	Effects at LOEL or Lowest Dose	Reference
90-Day Feeding	rat	10, 19, 38, 75, 150 or 300 mg/kg (by gavage)	NOAEL - 10 mg/kg LOEL - 19 mg/kg	Lesions of forestomach in female rats at 19 mg/kg	Abdo et al., 1984b
90-Day Feeding	mouse	19, 38, 75, 150 or 300 mg/kg (by gavage)	NOAEL - 19 mg/kg LOEL - 38 mg/kg	Lesions of forestomach in both sexes at 38 mg/kg	Abdo et al., 1984
14-Week Inhalation Toxicity	rat	0.01, 0.05 and 0.2 ppm (5 days/week)	NOAEL - 0.2 ppm LOEL - NE	No statistically significant effects	Rand et al., 1982
14-Week Inhalation Toxicity	monkey	0.01, 0.05 and 0.2 ppm (5 days/week)	NOAEL - 0.2 ppm LOEL - NE	No effects noted	Alexander et al., 1980

NE = Not established

monkeys weighing 1.5-2.5 kg (average 2.0 kg), were exposed to HEX, 6 hours/day, 5 days/week, for 14 weeks. Levels of exposure were 0, 0.01, 0.05 and 0.20 ppm HEX. In monkeys, there were no mortalities, adverse clinical signs, weight gain changes, pulmonary function changes, eye lesions, hematologic changes, clinical chemistry abnormalities or histopathologic abnormalities at any dose level tested.

Male rats in this study (Rand et al., 1982) had a transient appearance of dark-red eyes at 0.05 and 0.2 ppm HEX. At 12 weeks, there were marginal, but not statistically significant, increases in hemoglobin concentration and erythrocyte count in 0.01 ppm males, 0.05 ppm females and 0.20 ppm males and females. There were no treatment-related abnormalities in gross pathology or histopathology.

3.2. CHRONIC

3.2.1. Oral. The chronic oral toxicity of HEX has not been determined. The longest oral study to date was the previously reviewed work of Abdo et al. (1984).

3.2.2. Inhalation. Treon et al. (1955) exposed guinea pigs, rabbits, rats and mice to a concentration of 0.33 ppm for 7 hours/day, 5 days/week for 25-30 exposures. Guinea pigs survived 30 exposures; however, rats and mice did not survive 5 exposures, and 4/6 rabbits did not survive 30 exposures. Using a lower concentration (0.15 ppm HEX), guinea pigs, rabbits and rats survived 150 7-hour exposure periods. This level was too high for a chronic level study in mice since 4/5 animals did not survive. Slight renal and hepatic degeneration was noted in all species; mice, rats and guinea pigs also developed lesions in the lungs.

A 30-week chronic inhalation study of technical grade HEX (96%) in rats was conducted by Shell Toxicology Laboratory (Clark et al., 1982a). Four groups of 8 male and 8 female Wistar Albino rats were exposed to HEX at nominal concentrations of 0, 0.05, 0.1 and 0.5 ppm for 6 hours/day, 5 days/week, for 30 weeks and were observed for a 14-week recovery period without HEX exposure. At the highest dose level, 4 males and 2 females died. In males, there was depressed body weight gain in the 0.5 ppm group relative to controls beginning at 7 weeks of exposure and persisting throughout the remainder of the study. Females in the medium and high dose groups had lower body weights at the end of the recovery period as compared with controls. At 0.5 ppm, pulmonary degenerative changes were noted in both sexes although the males were affected more severely. At the highest dose, there were mild degenerative changes in the liver and kidneys at 30 weeks in a few rats and kidney weights were significantly increased in the females. After 30 weeks of study, there was no biologically significant toxicity noted in animals exposed to concentrations of 0.05 or 0.1 ppm HEX (Clark et al., 1982a).

A chronic inhalation study has been scheduled by the National Toxicology Program (Abdo, 1983).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. The teratogenic potential of HEX was evaluated in pregnant Charles River CD rats that were administered HEX (98.25%) by gastric intubation in corn oil at dose levels of 3, 10 and 30 mg/kg/day from days 6-15 of gestation. A control group received the vehicle (corn oil) at a dose volume of 10 ml/kg/day. Survival was 100%, and there was no difference in mean maternal body weight gain between dosed groups and controls. There were no differences in the mean number of implantations, corpora lutea, live

fetuses, mean fetal body weights or male/female sex ratios among any of the groups; and there were no statistical differences in malformation or developmental variations compared with the controls when external, soft tissue and skeletal examinations were performed (IRDC, 1978).

Murray et al. (1980) evaluated the teratogenic potential of HEX (98%) in CF-1 mice and New Zealand White rabbits. Mice were dosed at 0, 5, 25 or 75 mg/kg/day HEX by gavage from days 6-15 of gestation, while rabbits received the same dose from days 6-18 of gestation. The fertility of both the treated mice and the rabbits was not significantly different from the control groups. In the mice, no evidence of maternal toxicity, embryotoxicity or teratogenic effects was observed. A total of 249-374 fetuses (22-33 litters) were examined in each dose group.

In rabbits, maternal toxicity was noted at 75 mg/kg/day (diarrhea, weight loss and mortality), but there was no evidence of maternal toxicity at the lower levels. There were no embryotoxic effects at any dose level. Although there was an increase in the proportion of fetuses with 13 ribs at 75 mg/kg/day over controls, this was considered a minor skeletal variation, and the authors concluded that HEX was not teratogenic at the levels tested.

3.3.2. Inhalation. Studies on the teratogenic potential of inhaled HEX were not located in the review of the scientific literature.

There were no studies located in the literature that addressed other reproductive effects from exposure to HEX.

3.4. TOXICANT INTERACTIONS

In the review of available literature, HEX has not been shown to interact with other compounds. However, in many experiments on absorption of HEX, some common observations have been ascertained regarding HEX and living tissue. Repeated exposure of several animal species to levels of HEX vapor

in the 0.1-0.2 ppm range has been found to cause pulmonary degenerative changes (Treon et al., 1955; Clark et al., 1982a). The interaction of HEX within human tissue has caused mild degenerative changes in the kidneys, liver, brain, heart and adrenal glands.

There are insufficient data to identify clearly the site most sensitive to prolonged, repeated exposure of HEX. However, researchers found in comparing routes of administration over a wide variety of doses and lengths of exposures that, regardless of which route was used, damage to the lungs occurred (Lawrence and Dorrough, 1982). When HEX is administered orally to animals, the kidneys may be the most sensitive site, since subchronic dosing of rats and mice was found to cause nephrosis. Although the oral route may not be significant in human exposure, the fact that the kidneys are a possible target organ in subchronic exposure indicates that low-level, prolonged systemic exposure from any ambient route may affect the kidneys.

4. CARCINOGENICITY

4.1. HUMAN DATA

Mortality studies have been conducted on workers involved in the production of HEX or formulation of HEX products. The Shindell and Associates (1980) report was a cohort study of workers employed at the Velsicol Chemical Corporation plant at Marshall, IL between 1946 and 1979. The analysis showed no significant differences in mortality rates between these employees and the United States population.

Wang and MacMahon (1979) conducted a study on a group of 1403 males employed in plants producing or using HEX. The SMR was used to compare the workers with the general population. The two highest SMRs were 134 for lung cancer and 183 for cerebrovascular disease, but only the latter was statistically significant. The authors noted that these effects were unrelated to exposure because the deaths showed no consistent pattern with duration of employment or with duration of follow-up.

Other studies (Shindell and Associates, 1981; Buncher et al., 1980) showed similar results. In all of these studies, no carcinogenic effects of HEX exposure were noted.

4.2. BIOASSAYS

There are no animal bioassay data indicating that HEX is carcinogenic to animals by any route of exposure. An inhalation carcinogenesis bioassay in rats and mice is being conducted by NTP (Abdo, 1983).

4.3. OTHER RELEVANT DATA

4.3.1. Mutagenicity. Goggelman et al. (1978) found that HEX was not mutagenic before or after liver microsomal activation at 2.7×10^{-3} M in an Escherichia coli K₁₂ back mutation system. In this test there was 70% survival of bacteria at 72 hours. HEX was not tested at higher concentrations because it was cytotoxic to E. coli. An earlier report by Greim et

al. (1977) from the same laboratory indicated that HEX was also not mutagenic in Salmonella typhimurium strains TA1535 (base-pair mutant) or TA1538 (frame shift mutant) after liver microsomal activation; however, no details of the concentrations tested were given. Although tetrachlorocyclopentadiene is mutagenic in these systems, probably through metabolic conversion to the dienone, it appears that the chlorine atoms at the C-1 position of HEX hindered metabolic oxidation to the corresponding acylating dienone (Greim et al., 1977).

A study conducted by Industrial Bio-Test Laboratories (IBT, 1977) also suggests that HEX is not mutagenic in S. typhimurium. Both HEX and its vapors were tested with and without metabolic activation. The vapor test was done in desiccators with only the TA100 strain of S. typhimurium. It is not clear from the presented data of the vapors test that sufficient amounts of HEX or adequate times of exposure were used. Exposure times of 30, 60 or 120 minutes were studied. Longer exposures in the presence of the HEX vapors may be necessary for observation of a potential mutagenic effect. The statement in the text that testing was conducted in the toxic range is not supported convincingly by the investigators' results.

At concentrations of up to 1.25×10^{-3} $\mu\text{g}/\text{mL}$ in the presence of an S-9 liver activating system, HEX was not mutagenic in the mouse lymphoma mutation assay. Mutagenicity could not be evaluated at higher concentrations because of the cytotoxicity of HEX (Litton Bionetics, Inc., 1978b). This assay uses L5178Y cells that are heterozygous for thymidine kinase (TK+/-) and are bromodeoxyuridine (BUDR) sensitive. The mutation is scored by cloning with BUDR in the absence of thymidine. HEX is highly toxic to these cells, particularly in the absence of an activating system (at 4×10^{-5} $\mu\text{L}/\text{mL}$); a positive control, dimethylnitrosamine, was mutagenic at 0.5 $\mu\text{L}/\text{mL}$.

Williams (1978) found that HEX (10^{-6} M) was inactive in the liver epithelial culture hypoxanthine-guanine-phosphoribosyl transferase locus/mutation assay. At 10^{-5} M HEX also failed to stimulate DNA repair synthesis in hepatocyte primary cultures. Negative results were also obtained in an additional unscheduled DNA synthesis assay (Brat, 1983).

Two recent studies provided by NTP (Juodeika, 1983) also failed to demonstrate the mutagenicity of HEX. In *S. typhimurium* strains TA98, TA100, TA1535 and TA1537, levels of up to 3.3 μ g/plate were not mutagenic without activation and levels of up to 100.0 μ g/plate were not mutagenic after microsomal activation. Higher levels could not be tested because of excessive bacterial mortality. In the *Drosophila* sex-linked recessive lethal test, HEX was not mutagenic. The doses used in this study were 40 ppm by feeding for 3 days or by a single injection of 2000 ppm.

HEX has also been assayed in the mouse dominant lethal test (Litton Biogenetics, Inc., 1978a). In this assay, 0.1, 0.3 or 1.0 mg/kg HEX was administered by gavage to 10 male CD-1 mice for 5 days and these mice were then mated throughout spermatogenesis (7 weeks). This test determines whether the compound induces lethal genetic damage to the germ cells of males. There was no evidence of dominant lethal activity at any dose level by any parameter; e.g., fertility index, implantations/pregnancy, average resorptions/pregnancy. In this study, the highest dose used was the LD₅, determined by a 5-day mortality study in male CD-1 mice.

4.4. WEIGHT OF EVIDENCE

No reports of carcinogenicity of HEX have been found in the available literature. The data base is neither extensive nor adequate for assessing the carcinogenicity of HEX. The National Toxicology Program has recently completed a subchronic animal study and is conducting a chronic animal

inhalation bioassay using both rats and mice (Abdo, 1984). Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) for evaluating the overall weight of evidence, HEX is most appropriately considered a Group D - Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

5.1. OCCUPATIONAL STANDARDS

There is no current Occupational Safety and Health Administration (OSHA) standard for HEX levels in the workplace. However, the ACGIH (1982) has adopted a TLV, expressed as an 8-hour TWA of 0.1 mg/m³ (0.01 ppm). A STEL, the maximum allowable concentration in a 15-minute period, of 0.3 mg/m³ (0.03 ppm) for HEX has also been adopted (ACGIH, 1982). The levels are based on Treon et al. (1955).

NIOSH (1978) classified HEX as a Group II pesticide and recommended criteria for standards for occupations in pesticide manufacturing and formulating. These standards rely on engineering controls, work practices and medical surveillance programs, rather than workplace air limits, to protect workers from the adverse effects of pesticide exposure in manufacturing and formulating (NIOSH, 1978).

5.2. TRANSPORTATION REGULATIONS

The Hazardous Materials Transportation Act specifies the requirements to be observed in the preparation for shipment and transport of hazardous materials. The transport of HEX by air, land and water is regulated by these statutes, and the Department of Transportation has designated HEX as a "hazardous material," a "corrosive material" and a "hazardous substance." The maximum net quantity for transport by passenger-carrying aircraft or railcar has been set at 10 gallons per package. Transport on deck or below deck by cargo vessel is also permitted.

5.3. SOLID WASTE REGULATIONS

Under the Resource Conservation and Recovery Act (RCRA), the U.S. EPA has designated HEX as a hazardous toxic waste, Hazardous Waste No. U 130, subject to disposal and permit regulations (40 CFR 262-265 and 122-124).

5.4. FOOD TOLERANCES

Under the Federal Insecticide Fumigant and Rodenticide Act (FIFRA), a tolerance of 0.3 ppm has been established for chlordane residues, which are not to contain >1% of HEX (40 CFR 180.122).

5.5. WATER REGULATIONS

Under Section 311 of the Federal Water Pollution Control Act, the U.S. EPA designated HEX as a hazardous substance and established an RQ of 1 pound (0.454 kg) for HEX. Discharges equal to or greater than the RQ into or upon United States waters are prohibited unless the discharge is in compliance with applicable permit programs.

Under the Clean Water Act, the U.S. EPA has designated HEX as a toxic pollutant (i.e., priority pollutant). Effluent limitations guidelines, new source performance standards, and pretreatment standards have been developed or will be developed for the priority pollutants for 21 major industries.

Under the Clean Water Act, Ambient Water Quality Criteria (AWQC) for HEX were also developed (U.S. EPA, 1980a). Based on available toxicity data for the protection of public health, the level derived was 206 µg/l.

Using organoleptic data for controlling undesirable taste and odor of ambient water, the estimated level was 1 µg/l (U.S. EPA, 1980a).

5.6. AIR REGULATIONS

HEX is not regulated under the Clean Air Act.

5.7. OTHER REGULATIONS

Pursuant to rules under sections 8(a) and 8(d) of the Toxic Substances Control Act, all manufacturers of HEX are required to report health and safety information on HEX to EPA's Office of Toxic Substances. The deadline for submission of Preliminary Assessment Information Manufacturer's Report on HEX was November 19, 1982.

In 1979, the Interagency Testing Committee recommended that HEX be considered for health and environmental effects testing under Section 4(a) of the TSCA (44 FR 31866). This recommendation was based on evidence of potential human exposure and a potential for environmental persistence and bioaccumulation. The U.S. EPA (1982) responded in the Federal Register. The following is the statement from that notice:

EPA has decided not to initiate rulemaking to require testing of HEX under section 4 of TSCA because EPA does not believe that there is a sufficient basis to find that current manufacture, distribution in commerce, processing, use or disposal of HEX may present an unreasonable risk of injury to the environment or of mutagenic and teratogenic health effects. Neither has the EPA found evidence that there is substantial or significant environmental release of HEX. In addition, certain new studies have become available since the ITC's report or are underway, making additional testing for chronic and oncogenic effects unnecessary.

6. RISK ASSESSMENT

Pertinent risk assessment data are summarized in the Appendix of this report.

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Short-term studies by IRDC (1978) and Abdo et al. (1984) provide information on oral toxicity to rats and mice; however, the study sizes were small (5 and 10 animals/dose group, respectively). The studies by Abdo et al. (1984) are the only short-term studies yielding no-adverse-effect levels. Based upon the rat and mouse data, these short-term oral studies indicate a lowest-effect level for daily exposure to be 19 and 38 mg/kg, respectively. Multiplying by 5/7 to estimate a continuous exposure expanded from treatment on 5 days/week results in estimates of 13.6 and 27.14 mg/kg/day, respectively. The NOAELs estimated for continuous exposure for the rat and mouse were 7 and 14 mg/kg/day, respectively. Using the rat NOAEL of 7 mg/kg/day an AIS can be calculated. For a 70 kg man, an AIS for HEX by oral exposure would be $7 \text{ mg/kg/day} \times 70 \text{ kg} \div 100 = 4.9 \text{ mg/day}$. Division by 100 represents an uncertainty factor of 10, introduced for interspecies extrapolation, combined with another uncertainty factor of 10 in an attempt to protect unusually sensitive populations.

6.1.2. Inhalation. In 14-week inhalation studies a NOAEL for cynomolgus monkeys of 0.2 ppm HEX was established when exposures were 6 hours/day, 5 days/week. This same concentration was determined to be a NOAEL for rats using the same exposure regimen.

Using a monkey respiratory volume of $1.4 \text{ m}^3/\text{day}$, a daily exposure estimate can be calculated as follows: $2.27 \text{ mg/m}^3 \text{ (0.2 ppm)} \times 1.4 \text{ m}^3/\text{day} \times 6/24 \times 5/7 = 0.568 \text{ mg/day}$. Dividing this exposure estimate by 2.0 kg, the average body weight of the monkeys used in this experiment,

applying an uncertainty factor of 100 and multiplying by 70 kg, the assumed body weight of an average human, results in an AIS for inhalation exposure of 0.2 mg/day for a human. This AIS assumes that exposure will be uniformly distributed over the day.

An RQ has been calculated for the effect of mortality in mice exposed by inhalation to 0.15 ppm (1.7 mg/m³) HEX, 7 hours/day, 5 days/week for up to 150 exposures (Treon et al., 1955). A human MED was calculated by expanding to continuous exposure, assuming a human inhalation rate of 20 m³/day and an inhalation absorption coefficient of 0.5, and applying an uncertainty factor of 10 to extrapolate from subchronic to chronic data. A human MED of 0.35 mg/day was calculated, which corresponds to an RV_d of 6.2. Mortality is assigned an RV_e of 10. The CS of 62 was obtained as the product of RV_d and RV_e.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. No chronic oral toxicity evaluations of HEX were located which could be used for risk assessment purposes. Based on subchronic oral data (Abdo et al., 1984) an AIC of 0.49 mg/man/day for oral exposure is estimated by application of an additional uncertainty factor of 10.

6.2.2. Inhalation. Treon et al. (1955) exposed rats, guinea pigs, rabbits and mice to 0.15 ppm HEX 7 hours/day, 5 days/week for up to 7 months. No effects were seen in any species except mice: 4/5 mice died before the end of the exposure period. The dose-response relationship appears to be very steep in an earlier segment of the Treon et al. (1955) report. Exposure to 0.33 ppm HEX resulted in the death of 4/6 rabbits before 25 exposure sessions were completed; no rats or mice survived 20 exposure periods and guinea pigs survived the planned series of 30 exposures.

Clark et al. (1982a) exposed groups of Wistar rats (8/sex/dose) to HEX concentrations of 0, 0.05, 0.1 or 0.5 ppm 6 hours/day, 5 days/week for 30 weeks followed by a 14-week recovery period. At the 0.5 ppm exposure level, 4 males and 2 females did not survive and body weights were depressed in both sexes; pulmonary degenerative changes were noted, with males more severely affected. Mild degenerative changes were seen in the livers and kidneys, and kidney weights were elevated in females. At 0.1 ppm female body weights were depressed. No effects were noted at 0.05 ppm.

The reason for the discrepancy between these studies is unclear. Treon et al. (1955) reported 100% mortality in rats exposed to 0.33 ppm for 20 6-hour exposure sessions. In contrast, Clark et al. (1982a) exposed rats for 0.5 ppm for 30 weeks and noted 50% mortality in males and 25% mortality in females. Some differences may be attributable to the purity of the compound. Clark et al. (1982a) reported that the compound was 96% pure, with hexachloro-1,3-diene and octachlorocyclopentene as impurities, while Treon et al. (1955) reported 89.5% purity with contaminants not identified. It would be helpful to have another study in mice with a compound of similar purity to that used by Clark et al. (1982a) in order to evaluate whether mice are, in fact, more sensitive to HEX.

Using the Clark et al. (1982a) data which defined a NOEL for the rat of 0.05 ppm (0.5 mg/m³), an exposure dose of 0.066 mg/kg/day can be estimated by assuming a rat ventilatory volume of 0.26 m³/day, a body weight of 0.35 mg and 100% absorption, and multiplying by 6 hours/24 hours and 5 days/7 days to estimate continuous exposure. Applying an uncertainty factor of 1000 (10 for interspecies conversion, 10 to reflect concern about discrepancies in the available data and 10 to protect especially sensitive members of the population) and multiplying by 70 kg, an assumed average

human body weight, results in an inhalation AIC of 0.00462 mg/day. This corresponds closely to that estimated from the TLV of 0.1 mg/m³. Using a human 8-hour ventilatory volume of 10 m³/8 hour workday and multiplying by 5 days/7 days and dividing by an uncertainty factor of 100 (10 to protect potentially more sensitive segments of the general population, 10 to reflect deficiencies in the available data base) would result in an estimated daily intake of 0.0071 mg/day based on the TLV. The AIC, in units of mg/day, makes an implicit assumption that exposure will be uniformly distributed over the day.

6.3. CARCINOGENIC POTENCY (q₁*)

There are no available data on the long-term effects of exposure to HEX. Because the NTP is testing HEX in a chronic bioassay, the U.S. EPA Carcinogen Assessment Group will defer any decision on the carcinogenicity of HEX until the completion of the bioassay.

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APPENDIX

Summary Table for Hexachlorocyclopentadiene

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	monkey	2 mg/m ³ for 14 weeks	NOEL	0.2 mg/day	Rand et al., 1982
AIC	rat	0.5 mg/m ³ for 30 weeks	NOEL	0.0046 mg/day	Clark et al., 1982a
Maximum composite score	mice	0.15 ppm (1.7 mg/m ³) 7 hours/day, 5 days/week for up to 150 exposures RV _d =6.2)	mortality (RV _e =10)	62	Treon et al., 1955
Oral					
AIS	mouse	27.1 mg/kg/day for 13 weeks	forestomach hyperplasia	4.9 mg/man/day	SRI, 1981a
AIC				ND	

ND = Not determined